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<b>(21) International Application Number:</b> PCT/US87/03475  <b>(22) International Filing Date:</b> 23 December 1987 (23.12.87)  <b>(71) Applicant:</b> THE UNIVERSITY OF KENTUCKY RE- SEARCH FOUNDATION [US/US]; Kinkead Hall, Lexington, KY 40506-0057 (US).  <b>(72) Inventors:</b> DELUCA, Patrick, P. ; 3292 Nantucket Drive, Lexington, KY 40502 (US). KANKE, Motoko ; Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama-shi, Hiroshima-ken 720-02 (JP). SATO, Toyomi ; 4-22-10, Higashi Nippo- ri, Arakawa-ku, Tokyo 116 (JP). SCHROEDER, Hans, G. ; 1402 Flair, Encinita, CA 92024 (US).  <b>(74) Agents:</b> STEPNO, Norman, H. et al.; Burns, Doane, Swecker & Mathis, The George Mason Building, Washington & Prince Streets, P.O. Box 1404, Alexan- dria, VA 22313-1404 (US).		<b>(81) Designated States:</b> AT (European patent), AU, BE (Eu- ropean patent), CH (European patent), DE (Euro- pean patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European pa- tent), NL (European patent), SE (European patent).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> POROUS MICROSPHERES FOR DRUG DELIVERY AND METHODS FOR MAKING SAME  <b>(57) Abstract</b>  Controlled release drug delivery systems comprised of spherical microporous polymeric network of interconnecting channels containing pore incorporated drugs or other agents wherein the drugs or agents are confined within the pore channel are described. Also disclosed are processing parameters in connection with the novel method of the invention for obtaining drug delivery system especially suited for parenteral as well as oral administration.		

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POROUS MICROSPHERES FOR DRUG DELIVERY  
AND METHODS FOR MAKING SAME

BACKGROUND OF THE INVENTION

(1) Field of the Invention

5           The present invention relates generally  
to spherical polymer matrices for the controlled  
release of various drug(s) or other selected agents.  
More particularly, this invention describes  
methodology for preparing highly porous spherical  
10   polymer matrices with preselected incorporated agents,  
e.g., therapeutics, dispersed within the confines of  
the pores therein for controlled delivery to target  
physiological systems and resulting biodegradable  
microspheric drug carrier or controlled delivery  
15   systems.

(2) State of the Art

          A wide variety of microencapsulation drug  
delivery systems have been developed heretofore for  
the rate controlled release of therapeutics or other  
20   agents. For instance, considerable research has been  
devoted to incorporating therapeutic agents into  
polyesters such as poly( $\epsilon$ -caprolactone), poly( $\epsilon$ -  
caprolactone-CO-DL-lactic acid), poly(DL-lactic acid),  
poly(DL-lactic acid-CO-glycolic acid) and poly( $\epsilon$ -  
25   caprolactone-CO-glycolic acid) in which release was  
diffusion controlled. See, for example, Pitt, C.G.  
(Pitt, C.G., Gratzl, M.M., Jeffcoat, A.R., Zweidinger,  
R., Schindler, A., Sustained Drug Delivery Systems.

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II. Factors Affecting Release Rates from Poly( $\epsilon$ -caprolactone) and Related Biodegradable Polyesters. J. Pharm. Sci., 68, 1534 (1979). These systems were fabricated as films and capsules and the results suggest that the devices can be prepared to erode after release of the drug is essentially completed. Degradation of at least the polyesters has been reported to proceed by random hydrolytic cleavage of ester linkages by an autocatalytic process the rate of chain cleavage being influenced by chemical and morphological factors.

Sustained release systems of antimalarial agents and sulfadiazine in glycolic-lactic acid copolymers have also been reported. Wise, D.L., Gesser, J.D., McCormick, G.J., Sustained Release of a Dual Antimalarial System, J. Pharm. Pharmacol., 31, 201 (1979). Wise, D.L., McCormick, G.J., Willet, G.P., Anderson, L.C., Sustained Release of an Antimalarial Drug Using a Copolymer of Glucolic/Lactic Acid, Life Sci., 19, 867 (1976). Wise, D.L., McCormick, G.J., Willet, G.P., Anderson, L.C., Howes, J.F., J. Pharm. Pharmacol., 30, 686 (1978). Methods reported by the foregoing investigators involved dissolving the agents in a suitable solvent and either spray drying or casting films according to usual methods and evaporating the solvent. Various narcotic antagonists and steroids have been incorporated in films and implanted in rats [e.g., see Woodland, J.H.R., Yolles, S., Blake, D.A., Helrich, M., Meyer, F.J., Long-Acting Delivery Systems for Narcotic Antagonists: I. J. Med. Chem., 16, 897 (1973). Jackanicz, T.M., Nash, H.A., Wise, D.L., Gregory, J.B., Polylactic Acid as a Biodegradable

Carrier for Contraceptive Steroids, Contraception, 8,  
227 (1973). Anderson, L.C., Wise, D.L., Howes, J.F.,  
An Injectable Sustained Release Fertility Control  
System, Contraception, 13, 375 (1976)] and  
5 incorporated into particles injected subcutaneously  
[Yolles, S., Time-Release Depot for Anticancer Drugs:  
Release of Drugs Covalently Bonded to Polymers, J.  
Parent, Drug Assoc., 32, 188 (1978)]. The release of  
a number of anti-tumor agents has been evaluated in  
10 implantable systems as reported in Yolles, S., Time-  
Release Depot for Anticancer Drugs: Release of Drugs  
Covalently Bonded to Polymers, J. Parent, Drug Assoc.,  
32, 188 (1978), and the antibiotic Mitomycin C has  
been encapsulated in microspherical carriers of  
15 gelatin and administered intravenously [Yoshioka,  
T., Hashida, M., Muranishi, S., and Sezaki, H.,  
Specific Delivery of Mitomycin C to Liver, Spleen and  
Lung: Nano-and Microspherical Carriers of Gelatin.  
Intern J. Pharm., 81, 131 (1981)] and the effect of  
20 size on in vivo distribution and the potential for  
antibiotic targeting discussed. The size distribution  
of the microspheres (i.e. 5-30  $\mu$ m) reported in the  
last mentioned publication was very broad, especially  
for intravenous administration. Recently the in-vitro  
25 release of local anesthetics from polylactic acid  
spheres prepared by a solvent evaporation process has,  
likewise, been reported [Wakiyama, N., Kaxuhiko, J.,  
Nakano, M., Influence of Physicochemical Properties of  
Polylactic Acid on the Characteristics and In Vitro  
30 Release Patterns of Polylactic Acid Microspheres  
Containing Local Anesthetics, Chem. Pharm. Bull., 30,  
2621 (1982)]. The patterns of release from these  
polylactic acid spheres were characterized by the  
various degrees of degradation of the polymer as well

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as solubilities of loaded drugs although no attempt was apparently made to evaluate this parameter. Additionally, it is apparent that the solubility of the drug played an important role in the rate and extent of release. Scanning electron photomicrographs also revealed varying degrees of erosion and deformation of the spheres after release.

It will be seen from the foregoing that while the controlled release delivery of pharmaceuticals or other agents from heretofore described polymeric systems has been principally limited to oral, topical or implantable systems in which the considerations relative to pore size and/or cell size within the carrier matrix as well as the overall dimensions of the microspheres to be administered along with the rate of release and the relative absorption rate from a bioavailability standpoint are distinctly different from the evaluation parameters involved in the utilization of these microsphere delivery systems for parenteral, i.e., intravenous, intraarterial, intraocular or inhalation administration routes to which the present invention is particularly applicable.

#### SUMMARY OF THE INVENTION

It is, therefore, a primary object of the present invention to afford novel porous microspheres for the controlled delivery of drugs or other matrix confined materials to target organs or systems in warm-blooded animals in need thereof and to methods for making such microspheres.

A further object of the present invention is to provide methods for preparing porous microspheres of heretofore unattainable narrow-range size distribution particularly suitable for use as  
5 parenterally administerable drug delivery systems for injectable and inhalation dosage forms as well as facilitating sustained drug release via more conventional oral administration routes.

It is a still further object of the present  
10 invention to provide porous microsphere matrices wherein the accessibility of the drug or other incorporated agent is not dependent upon the physical or chemical erosion of the polymer for release.

Another object of the present invention is to  
15 provide chemically modified polymer compositions suitable for use in the spherical polymer matrices of the invention whereby porosity as well as degradation of the polymer substrate after release of the matrix confined agent for release can be predetermined and  
20 controlled.

A still further object of the present invention is to provide porous polymeric microspheric drug delivery systems which allow targeting of drugs or other agents to specific host tissues or cells via  
25 injection or inhalation providing high localized concentrations, sustained activity, systemic administration and treatment not possible by other methods thereby minimizing undesirable systemic effects of toxic drugs administered directly into the  
30 circulation.

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These and other similar objects, advantages and features are accomplished according to the methods, products and compositions of the present invention.

5

BRIEF DESCRIPTION OF DRAWINGS

FIGURE 1 is a drawing of a polymer with a low degree of crystallinity in accordance with the practice of the present invention and a drawing of a polymer with a high degree of crystallinity.

10

FIGURE 2 is a graph of half-life in months versus various ratios of polyglycolic (PGA) and polylactic (PLA) as copolymer implanted in rat tissues.

15

FIGURE 3 is a graph of percent water uptake versus percent glycolic acid for glycolide/lactide copolymers.

FIGURES 4 and 4A generally depict the preparative methods of the present invention.

20

FIGURE 5 depicts the shape and surface appearance of polyglycolic (PGA) microspheres prepared by Dilution-Precipitation Method.

FIGURE 6 depicts the shape and surface appearance of PGA microspheres prepared by Freeze Dry Method.

25

FIGURE 7 is a graph of the release profile from matrices which were prepared by Precipitation Method and contain different amounts of marker.



FIGURE 8 is a graph of the release profile from matrices which were prepared by Freeze Dry Method and contain different amounts of marker.

5      FIGURE 9 is a graph of the release profile from matrices which were prepared by Freeze Dry Method and contain prednisolone acetate.

10      FIGURE 10 depicts scanning electron micrography (SEM) micrographs of the PGA matrix manufactured by Freeze Dry Method 72 hours following drug release.

FIGURE 11 depicts SEM micrographs of the PGA matrix manufactured by Freeze Dry Method after 120 hours following drug release.

15      FIGURE 12 depicts SEM micrographs of the PGA matrix manufactured by Freeze Dry Method 168 hours following drug release.

FIGURE 13 is a graph of the release of dye from polymer in plasma.

20      FIGURE 14 depicts PGL microspheres containing blue dye manufactured by Dilution-Precipitation Method.

FIGURE 15 depicts gelatin microspheres manufactured by a modified Dilution-Precipitation Method.

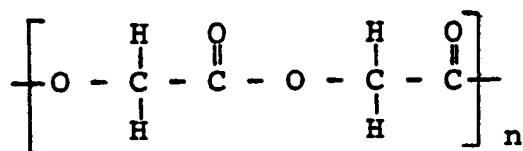
25      DESCRIPTION OF THE PREFERRED EMBODIMENTS

The porous polymeric microspheres of the present invention are derived from copolymeric and homopolymeric polyesters containing hydrolyzable ester linkages which are, therefore, biodegradable.

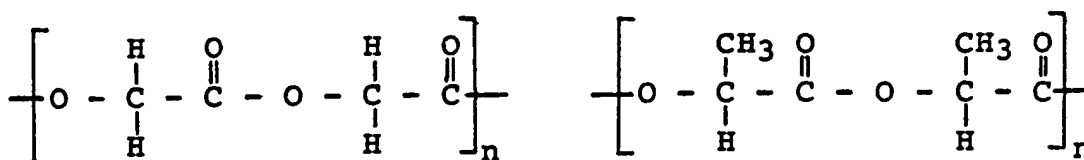
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Typically preferred of such polyesters are polyglycolic (PGA) and polylactic (PLA) acids, and copolymers of glycolide and L(-lactide) (PGL). The  
aforementioned polyesters are particularly suited for  
the methods and compositions of the present invention  
by reason of their characteristically low human  
toxicity and virtually complete biodegradability. Of  
course, it will be understood that the particular  
polyester or other polymer, oligomer, copolymer, etc.,  
utilized as the microspheric polymer matrix is not  
critical and a variety of polymers may be utilized as  
a consequence of the novel processing methods of the  
invention which yield the desired microspheres of the  
porosity, consistency, shape and size distribution  
essentially irrespective of the source of polymer  
utilized. Accordingly, other biodegradable or  
bioerodable polymers or copolymers evidencing the  
necessary low degree of toxicity suitable for use in  
the present invention include, for example, gelatin,  
agar, starch, arabinogalactan, albumin, collagen,  
natural and synthetic materials or polymers, such as,  
poly( $\epsilon$ -caprolactone), poly( $\epsilon$ -caprolactone-CO-lactic  
acid), poly( $\epsilon$ -caprolactone-CO-glycolic acid),  
poly( $\beta$ -hydroxy butyric acid), polyethylene oxide,  
polyethylene, poly(alkyl-2-cyanoacrylate), (e.g.,  
methyl, ethyl, butyl, etc.), hydrogels such as  
poly(hydroxyethyl methacrylate), polyamides (e.g.,  
polyacrylamide), poly(amino acids) (i.e., L-leucine,  
L-aspartic acid,  $\beta$ -methyl-L-aspartate,  $\beta$ -benzyl-L-  
aspartate, glutamic acid and the like),  
poly(2-hydroxyethyl DL-aspartamide), poly(ester urea),  
poly(L-phenylalanine/ethylene glycol/1,6-  
diisocyanatohexane) and poly(methyl methacrylate).

The foregoing exemplary natural and synthetic polymers suitable for use in the present invention are, of course, either readily available commercially or are obtainable by condensation polymerization reactions from the suitable monomers or, comonomers or oligomers. For instance, homopolymers and copolymers of glycolic and lactic acids can be prepared by direct polycondensation or by reacting glycolide and lactide monomers as disclosed by Gilding, D.K., Reed, A.M., Biodegradable Polymers for Use in Surgery - Polyglycolic/Poly(lactic acid) Homo- and Copolymers: 1, Polymer, 20, 1459 (1979). Structurally, polyglycolic acid (PGA) has the following structure:



whereas the related copolymer polyglycolic acid/polylactic acid (PGL) has the structure depicted below:



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Both of the foregoing are polyester type polymers which readily degrade via hydrolysis at the ester linkages and by appropriately selecting suitable molecular weight polyesters, modifying the degree of crosslinking and the degree of crystallinity, the biodegradation properties of such polymers may be advantageously controlled. As pointed out previously, however, in accordance with the present invention the necessity for biodegradation or bioerosion of the polymer matrix for release of the agent incorporated therein to occur is obviated by reason of the intrinsic porosity characteristics of the polymer matrices of the invention and the fact that the incorporated agent or agents are matrix confined within the interconnecting channels or pores of the spherical polymer. However, in accordance with alternative and preferred embodiments of the present invention the possibility that the matrix could be coated with a film or crosslinking agent to inhibit or control release, thereby allowing bioerosion to influence release is not in any way precluded and may, in fact, depending upon the nature of the incorporated agent as well as the rate of release required in the target organ system may be desirable or advantageous. For example, in those instances where it may be desirable to inhibit or retard drug release rates, more extensive cross-linking of the copolymer or polymer may be achieved by the addition of higher concentrations of suitable cross-linking agents such as glyoxal, succinaldehyde, glutaraldehyde, 3-methylglutaraldehyde, methyleneacrylamide, bisacrylamide and similar cross-linking agents. Likewise, the reduction or elimination of crosslinks in the copolymers or

polymers of the invention will result in enhanced biodegradability. On the basis of such polymer modifications, it is evident that the release of the incorporated agent or agents will be essentially  
5 complete, i.e., 90% before any erosion or degradation of the polymer matrix occurs, and, thus, the polymer composition can be preselected to permit controlled clearance from the target system after release of the incorporated drug.

10 The polymers utilized in accordance with the invention exist in the crystalline form with amorphous regions interdispersed between the crystalline areas as shown, for example, in Figure 1. Hydrolysis rates have been shown to be higher in the amorphous regions.  
15 For the copolymers of PLA/PGA, the degree of crystallinity is reduced at a composition of equal amounts of PLA and PGA. As shown in Figure 2, the half-life for the degradation of polymer in rat tissue was lowest at a 50-50 composition. Figure 3 shows  
20 that the water uptake is highest in this range which constitutes the amorphous region. Therefore bioerosion occurs in the amorphous regions initially and eventually the backbone is destroyed and the matrix will collapse, thereby accelerating the  
25 bioerosion and elimination of the polymer.

Consistent with the controlled conditions of the methods of the present invention, spherical polymer matrices or microspheres having a diameter range between about 0.5 to 150 microns ( $\mu\text{m}$ ) can be  
30 prepared in narrow size ranges for targeting to various organ or organ systems via parenteral injection or inhalation. A more preferred range for the spherical polymer matrices or microspheres is

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between 0.5 to 50 microns. The integratable methods for preparing porous spherical matrices consistent with the present invention result in microspheres in which essentially all of the agent(s) incorporated within the pores of the drug delivery system is readily available for release. Essentially the foregoing principle objective of the invention is accomplished by forming emulsified droplets or spheres consisting of a homogeneous mixture of polymer (or copolymer), solvent and matrix incorporated agent from a solution of a preselected polymer and agent dispersed in a continuous (non-solvent phase). Removal of the solvent from the sphere by either freeze drying or dilution-extraction-precipitation or a combination thereof creates the interconnecting network of pores wherein the incorporated agent is confined within the walls and channels of the pores as opposed to random distribution within the more poorly defined interstices of the polymer. As used in the specification and claims, the expression "pore incorporated agent" is used to define the relative specific location of the agent confined essentially completely inside the pores of the porous microspheres of the invention. Similarly, the term "agent" specifically encompasses any diagnostic or pharmacologically active material which would be generally classifiable as a drug suitable for introduction into a human or other warm-blooded animal host, as well as other materials or compositions including, for instance, dyes, antigens, antibodies, enzymes, flavors, comestibles and the like and mixtures thereof.

The drug delivery systems in accordance with the present invention are ideally suited for administration by parenteral or inhalation routes. It will be appreciated by those skilled in the art that the porous microspheres of the present invention containing pore incorporated drugs for release to target cells or tissues, therefore, may be administered alone or in admixture with appropriate pharmaceutical diluents, carriers, excipients or adjuvants suitably selected with respect to the intended route of administration and conventional pharmaceutical practices. For example, for parenteral injection, dosage unit forms may be utilized to accomplish intravenous, intramuscular or subcutaneous administration, and for such parenteral administration, suitable sterile aqueous or non-aqueous solutions or suspensions, optionally containing appropriate solutes to effectuate isotonicity, will be employed. Likewise for inhalation dosage unit forms, for administration through the mucus membranes of the nose and throat or bronchio-pulmonary tissues, suitable aerosol or spray inhalation compositions and devices will be utilized.

Consistent with other preferred embodiments of the present invention, the porous microspheric drug delivery systems of the invention may be additionally coated or modified to advantageously influence the targeting of the release of the incorporated drug therein to preselected target cells, tissues or organs. For example, the drug delivery microspheres may be coated with various agents, e.g., proteins, surfactants, antibodies or receptor site specific drugs which may be the same or different from those

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incorporated in the porous microsphere whereby the release of the incorporated drug is concentrated at the targeted system.

5       The preparative methods of the present invention are generally depicted in Figures 4 and 4A.

10       In accordance with the methods for making the porous microspheres of the invention, the desired polymer or copolymer and the drug(s) or other agent(s) are dissolved separately in a suitable solvent. The polymer and drug solutions are mixed together in the appropriate manner to provide a polymer concentration ranging between about 2.5 to 18% w/w and a drug:polymer ratio ranging between about 1:1 to 1:10. The temperature of the resultant solution is  
15       controlled between about 30-45°C. The drug-polymer solution comprising the dispersed phase is dispersed into the continuous phase containing an appropriate surface active agent at a thermostatically controlled temperature generally in the range of 10°-20°C. The  
20       foregoing is accomplished by forcing the dispersed phase under pressure through a fine orifice nozzle. The continuous phase which is 10-20 times by weight of the dispersed phase is then agitated by a dispersator. Following the introduction of the dispersed phase,  
25       one of two recovery methods (see Figure 4) is utilized to stabilize and recover the drug-loaded microspheres for final processing.

30       More specifically, consistent with the freeze-dry method of the invention, following dispersion, the temperature is maintained at 10-20°C, preferably 15°C, for two minutes then increased to 45-55°C, preferably 50°C, over a three minute period. Vigorous agitation of the mixture is continued during this period. When



the temperature reaches 50°C, either a refrigerant solution is circulated through the jacket from the bath or the container is immersed in dry ice-methanol and cooled to a temperature which will freeze the  
5 drug-polymer-solvent phase and not the continuous phase. The suspension or emulsion (solid dispersion phase in liquid continuous phase) is quickly transferred to precooled vials (-40° to -60°C) and cooled to -40° to -60°C in a freeze dryer, freezer or  
10 dry ice-acetone bath. The solvent in the suspended droplets (microspheres) and the continuous phase solvent are removed by freeze drying. Upon completion of the freeze dry cycle the microspheres are washed with a suitable solvent, filtered and air dried.

15 In the dilution-extraction-precipitation method of the invention, following dispersion, the temperature is maintained at 10-20°C, preferably 15°C, for two minutes, then increased to 45-55°C, preferably 50°C, over a three minute period. The dispersion is  
20 then transferred to a vessel containing a diluent solvent at room temperature as depicted in Figure 4. Agitation is continued for 30 minutes using a vibromixer. During the process the dispersed phase solvent is removed from the drug-polymer-solvent  
25 emulsion droplets by extraction causing solidification of the droplets. The solid spheres are then removed by filtration, washed with a suitable solvent and air dried.

30 Solvents for the dispersed phase and the continuous phase will of course differ in order to attain phase separation and, are therefore, selected based upon the solvent requirements for each phase. More particularly, the solvent for the dispersed

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phase should dissolve the polymer and the incorporated agent and remain in the emulsified droplets with the drug and polymer in the continuous phase until leached out by a diluent solvent or removed by vaporization or evaporation. In this way pores are formed in the drug-polymer matrix. In the case of PGA polymer into which water soluble markers or agents are incorporated, hexafluoroacetone sesquihydrate (HFA) is an appropriate solvent. Other solvents which can be used, depending upon characteristics of polymer and incorporated agents, include water, hexafluoroisopropanol (HFIP), methylene chloride, tetrahydrofuran, hexane, benzene and the like. Solvents for the continuous phase should not dissolve the polymer and should emulsify the dispersed phase. Solvents include benzene, dioxane, acetone, methylene chloride, chloroform, carbon tetrachloride, toluene, ethyl alcohol, acetonitrile, p-xylene, tetrahydrofuran and mixtures of these solvents.

A diluent (non-solvent) phase can also be employed to dilute the continuous phase following dispersion of the polymer-agent solution. The diluent should be miscible with the continuous phase and dispersed phase solvents but not dissolve the polymer or incorporated agent. Examples of solvents include 1,4-dioxane, cyclohexanone, acetone, ethanol, acetonitrile, dimethylformamide, tetrahydrofuran and cyclohexanol.

The concentration of polymer in the dispersed phase directly influences the porosity or "void" space in the final microsphere product as well as the shape of the microsphere. A concentration of 2.5% to 10% w/w polymer yields dimensionally suitable spherical

particles. With respect to the concentration of the pore incorporated agent, up to 50% by weight of the polymer has been achieved with consistent results.

5 In accordance with another preferred embodiment of the present invention, hydrophilic colloids are employed to improve the yield and prevent phase inversion in the continuous and diluent phases. Substances which can be utilized in concentrations ranging between about 0.5 to 5% include anionic  
10 surfactants such as sorbitan, gelatin and gelatin derivatives, polyvinyl alcohol, polystyrene sulfonate, hydroxyethylcellulose, hydroxypropylcellulose and related colloids with suitable hydrophilicity.

It has been determined that certain processing  
15 parameters influence the recovery methods as well as the resultant microspheres of the present invention. . Identifiable parameters include the concentration of polymer in the dispersed phase, the temperature of the dispersed phase at the time of dispersion, the  
20 concentration of surfactants in the dispersed phase as well as the ratio of incorporated agent to polymer in the dispersed phase. It will be appreciated that the concentrations, temperatures and ratios referred to hereinabove and in the Examples set forth operable  
25 ranges and that other numerical expressions may apply as different solvents, polymers, incorporated agents, etc. are selected.

The shape and surface appearance of  
microspheres prepared in accordance with the recovery  
30 methods of the invention were assessed by Scanning Electron Microscopy (SEM), Figures 5-6 as well as by optical micrography.

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Typical release profiles are also shown in Figures 7-9. The very water soluble FD&C dye Blue #1 releases within 1-3 days depending upon the concentration of dye (i.e., marker). In  
5 all instances release is completed before discernible degradation or erosion of the matrix occurs. Figures 10 and 11 show SEM micrographs of the spheres following 72 hours and 120 hours, respectively, in the dissolution media. The spheres were essentially  
10 intact indicating minimal erosion. The release of a less-soluble compound, prednisolone acetate is shown in Figure 9. Essentially 90% of the drug was released after 7 days and degradation of the matrix was very evident after 7 days as shown by the fragmentation in  
15 Figure 12.

The following non-limiting Examples are afforded in order that those skilled in the art may more readily understand the present invention and specific preferred embodiments thereof with respect to  
20 the methods and compositions in accordance with the foregoing description.

Example 1      FD&C Blue #1 - PGA microspheres (freeze dry recovery)

1. 0.1 g of FD&C Blue #1 was dissolved in 9.9 g of  
25 HFA to make a 1% (w/w) solution.
2. 1.0 g of PGA was dissolved in 9.0 g of HFA to make a 10% (w/w) solution.
3. Equal weights of the above are mixed together to form the dispersed phase. The resultant spheres  
30 from this combination are very porous having 94.5% "void" space and a dye-polymer ratio of 1:10. In this example 2.0 g of each solution were mixed

together and maintained at 37°C. The spherical microporous polymeric network has a degree of porosity of between about 80 to 98 percent as determined by relative void space in relation to the starting concentration of the polymer.

Dispersed Phase Concentrations:

DYE	POLYMER	SOLVENT
20 mg	200 mg	3780 mg
0.5%	5.0%	94.5%

4. The continuous phase constituted 160g of  $\text{CCl}_4$  containing 0.1% sorbitan sesquioleate (SO-15) which was maintained at 15°C in a 500 ml jacketed vessel. A dispersator was located at the center of the vessel for mixing.
5. The dye-polymer-solvent solution was then dispersed via pressure through a fine orifice into the continuous phase which was agitated vigorously with the dispersator. The temperature was maintained at 15°C and the mixing continued for 2 minutes. The temperature was then increased to 50°C over a 3 minute period by either circulating 70°C water through the jacket (or immersing the vessel in a 70°C water bath).

6. When the temperature reached 50°, a refrigerant solution at -22°C was circulated through the jacket to freeze the dispersed phase and not the continuous phase (f.p. of  $\text{CCl}_4$  = -22.6°).

- 5        7. The above suspension was quickly transferred to  
pre-cooled (ca -45°C) 50 ml vials and cooled to  
-40° to -50° on the shelves in a freeze dryer which  
had been precooled to -50°C.
- 10      8. The suspension was maintained at -50° for 1  
hour. Vacuum was applied and the shelves  
heated to -10°C and maintained at this  
temperature for 24 hours to remove the CCl<sub>4</sub>.  
The temperature of shelves was increased to  
20°C for 24 hours to remove the HFA. The  
15      temperature of the shelves was increased to  
35° and maintained for 2 hours to ensure  
removal of all solvent.
- 20      9. The vials containing the spheres were removed from  
the chamber and stoppered pending washing and  
evaluation.

Example 2      Prednisolone acetate - PGA microspheres  
(freeze dry recovery)

1. 0.1 g of prednisolone acetate was dissolved in 9.9 g of HFA to make a 1% w/w solution.
2. 1.0 g of PGA was dissolved in 9.0 g of HFA to make a 10% w/w solution.
3. 2.0 g of each solution were mixed together and maintained at 37°C.

Dispersed Phase Concentrations:

DRUG	POLYMER	SOLVENT
20 mg	200 mg	3780 mg
0.5%	5.0%	94.5%

4-9. Steps four through nine were the same as in Example 1.

Spheres obtained by the freeze dry method were washed twice with 125 ml volumes of acetone and collected on 0.8, 10, & 50  $\mu$ m filters. The spheres obtained by the precipitation method were washed with acetone in the size ranges previously obtained by filtration and collected on 0.8, 10, & 50  $\mu$ m filters. Washing removes approximately 8.5% of the dye or drug from the sphere.

Example 3 Characterization of Microporous Microspheres and Release of Model Compounds

SEM Photomicrographs of Examples 1 and 2 are shown in Figures 5-6 at 10-fold differences in magnification. The porous nature is evident from the topography of the magnified surfaces of both methods of preparation.

In-vitro release from the microspheres was determined in 0.1 M phosphate buffer (pH 7.4). The spheres were quantitatively transferred to a 15 ml cuvette tube with a screw cap and the buffer added. The tubes were placed on a rocker-type shaker in an oven at 37°C. The tubes were centrifuged at various

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times and solution samples were removed for spectrophotometric analysis at 630 nm for FD&C Blue #1 and at 245 nm for prednisolone acetate. Release profiles are shown in Figures 7-9 for Examples 1, 2 & 3 along with the profiles of other compositions. The release of water soluble dye was essentially complete in 2 to 3 days with spheres prepared by the dilution-extraction-precipitation and freeze dry methods while the less-soluble prednisolone acetate releases much more slowly, 90% in 7 days.

In experiments at a fixed level of dye, i.e., 4% (by weight of polymer) and variable polymer concentration in the dispersed phase (2.5%, 5% & 10%), the release rate was reduced in relation to the polymer concentration (Figure 13). The "void" space or the porosity is controlled by the polymer (or solvent) concentration of the dispersed phase.

Example 4      FD&C Blue #1 - PGL microspheres  
                  (Dilution-Extraction-Precipitation  
                  Recovery)

1. 0.1 g of FD&C Blue #1 was dissolved in 9.9 g of HFA to make a 1% (w/w) solution.
2. 0.5 g of polyglactin 910 (Vicryl<sup>R</sup>) was dissolved in 4.5 g of HFA to make a 10% (w/w) solution.
3. Equal weights of the above were mixed together to form the dispersed phase and maintained at 37°C.



Dispersed Phase Concentrations:

DYE	POLYMER	SOLVENT
20 mg	200 mg	3780 mg
0.5%	5.0%	94.5%

The resultant spheres from this combination ratio will be very porous having 94.5% "void" space and a dye-polymer ratio of 1:10.

- 5      4-5.      Steps four and five are the same as in Example 1.
- 6-8.      Steps six through eight are the same as in Example 2. See Figure 14 for topography of the microspheres.

10      Example 5      FD&C Blue #1 - Gelatin microspheres  
(Dilution-Extraction-Precipitation Recovery)

1. 0.1 g of FD&C Blue #1 was dissolved in 10.0 g of 10% w/w aqueous gelatin solution. 3.0 g of this mixture was maintained at 37°C as a dispersed phase.

Dispersed Phase Concentrations:

DYE	POLYMER	SOLVENT
30 mg	300 mg	2670 mg
1.0%	10.0%	89.0%

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2. The continuous phase constituted 120 g of  $\text{CCl}_4$  containing 2% S0-15 which was maintained at  $40^\circ$  in a 500 ml jacketed vessel. A dispersator was located at the center of the vessel for mixing.
- 5 3. 3.0 g of the dye-gelatin-water solution was dispersed via pressure through a fine orifice into the continuous phase which was agitated vigorously. The temp. was maintained at  $40^\circ\text{C}$  and the mixing continued for 3 min.
- 10 4. 100 g of 1,4-dioxane containing 2% S0-15 was added slowly to the emulsified dye-gelatin-water system in  $\text{CCl}_4$  to harden the gelatin matrix and agitation continued for 30 minutes.
- 15 5. A refrigerant solution was circulated through the jacket and the system cooled to  $14^\circ$ .
6. 50 g of a curing solution, consisting of 10 g of 50% glutaraldehyde and 40 g of 1,4-dioxane containing 2% S0-15, was added dropwise (4 ml/min) to the dye-gelatin-water system in  $\text{CCl}_4$ .
- 20 Agitation continued at  $14^\circ\text{C}$  for 30-60 minutes.
7. The suspension was then filtered through a series of filters to collect the spheres in various size ranges, followed by washing. See Figure 15 for topography of the microspheres.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and  
5 substitutions can be made therein without departing from the spirit of the invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow.

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WHAT IS CLAIMED IS:

1. A method for preparing a relatively homogeneous essentially spherical microporous polymeric network of interconnecting channels containing a pore incorporated agent therein comprising preparing an agent-polymer-solvent dispersed first phase, dispersing said first phase in a continuous solvent second phase to obtain a suspension, removing solvent from said suspension by freeze drying or dilution-extraction-precipitation, and recovering said microporous polymeric network.

2. The method according to claim 1 wherein said spherical microporous polymeric network is derived from a natural or synthetic copolymer or polymer selected from the group consisting of gelatin, agar, starch, arabinogalactan, albumin, collagen, polyglycolic acid, polylactic acid, glycolide-L(-) lactide, poly( $\epsilon$ -caprolactone), poly( $\epsilon$ -caprolactone-CO-lactic acid), poly( $\epsilon$ -caprolactone-CO-glycolic acid), poly( $\beta$ -hydroxy butyric acid), polyethylene oxide, polyethylene, poly(alkyl-2-cyanoacrylate), poly(hydroxyethyl methacrylate), polyamides, poly(amino acids), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane) and poly(methyl methacrylate).

3. The method according to claim 1 wherein said pore incorporated agent comprises a diagnostic or pharmacologically active drug.

4. The method according to claim 1 wherein the solvent in said first phase comprises an inorganic or organic solvent in which said agent-polymer are relatively soluble.

5           5. The method according to claim 4 wherein said solvent comprises water, hexafluoroisopropanol, methylenechloride, tetrahydrofuran, hexane, benzene, or hexafluoroacetone sesquihydrate.

10           6. The method according to claim 1 wherein said second solvent comprises a solvent for said continuous phase in which said first phase is emulsifiable.

15           7. The method according to claim 6 wherein said solvent comprises benzene, dioxane, acetone, methylenechloride, chloroform, carbon tetrachloride, toluene, ethyl alcohol, acetonitrile, p-xylene, tetrahydrofuran, or mixtures thereof.

20           8. The method according to claim 7 wherein said method further includes the step of employing a diluent-nonsolvent phase to dilute said continuous second solvent phase following dispersion of said agent-polymer-solvent dispersed first phase.

25           9. A method for preparing a relatively homogeneous essentially spherical microporous polymeric network of interconnecting channels containing a pore incorporated agent therein comprising preparing an agent-polymer-solvent dispersed first phase in which the concentration of said polymer ranges between about 2.5 percent to 18

-28-

percent w/w, and said agent-polymer ratio ranges between about 1:1 to 1:10, dispersing said first phase in a continuous solvent second phase by pressure forcing said first phase through a droplet forming  
5 orifice nozzle to obtain a suspension, removing solvent from said suspension by freeze drying or dilution-extraction-precipitation, and recovering said microporous network.

10. The method according to claim 1 further  
10 including the step of employing a hydrophilic colloidal material to prevent phase inversion.

11. The method according to claim 1 wherein said removal of solvent from said suspension is by dilution-extraction-precipitation whereby said  
15 dispersed first phase solvent is removed from said agent-polymer.

12. The method according to claim 1 wherein said agent-polymer solvent dispersed first phase is maintained at a temperature ranging between about 10  
20 to 20°C during said dispersing step.

13. A drug delivery system comprising a spherical microporous polymeric network of interconnecting channels containing a drug wherein said drug is distributed within the pores of said  
25 microporous polymeric network.

14. The drug delivery system according to claim 13 wherein said spherical microporous polymeric network is selected from the group consisting of gelatin, agar, starch, arabinogalactan, albumin,

collagen, polyglycolic acid, polylactic acid,  
glycolide-L(-)lactide copolymer, poly( $\epsilon$ -caprolactone),  
poly( $\epsilon$ -caprolactone-CO-lactic acid), poly( $\epsilon$ -  
5 caprolactone-CO-glycolic acid), poly( $\beta$ -hydroxy butyric  
acid), polyethylene oxide, polyethylene, poly(alkyl-2-  
cyanoacrylate), poly(hydroxyethyl methacrylate),  
polyamides, poly(amino acids), poly(2-hydroxyethyl  
DL-aspartamide), poly(ester urea), poly(L-  
10 phenylalanine/ethylene glycol/1,6-diisocyanatohexane)  
and poly(methyl methacrylate).

15           15. The drug delivery system according to  
claim 13 or 14 wherein said polymer comprises a  
polyester polymer of polyglycolic acid or polylactic  
acid or a co-polymer of glycolide and L(-)lactide.

15           16. The drug delivery system according to  
claim 15 wherein said polymer is biodegradable.

20           17. The drug delivery system according to  
claim 15 wherein said system is suitable for  
parenteral administration to a human host in need  
thereof.

18. The drug delivery system according to  
claim 13 wherein said spherical microporous polymeric  
network comprises microspheres between about 0.5 to  
150 microns in diameter.

25           19. The microspheres according to claim 18  
wherein said diameter ranges between 0.5 to 50  
microns.

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20. The drug delivery system according to claim 13 wherein said system comprises a sustained release system for the rate controlled release of drug to a specific target site.

5           21. The drug delivery system according to claim 13 wherein said spherical microporous polymeric network has a degree of porosity of between about 80 to 98 percent as determined by relative void space in relation to the starting concentration of polymer.

10           22. The drug delivery system according to claim 13 further comprising a coating on said spherical microporous polymeric network capable of promoting targeting of said drug containing microporous polymeric network to targeted cells or  
15 organ systems whereby said drug upon release from said drug delivery system acts predominantly upon the targeted cells or organ systems.

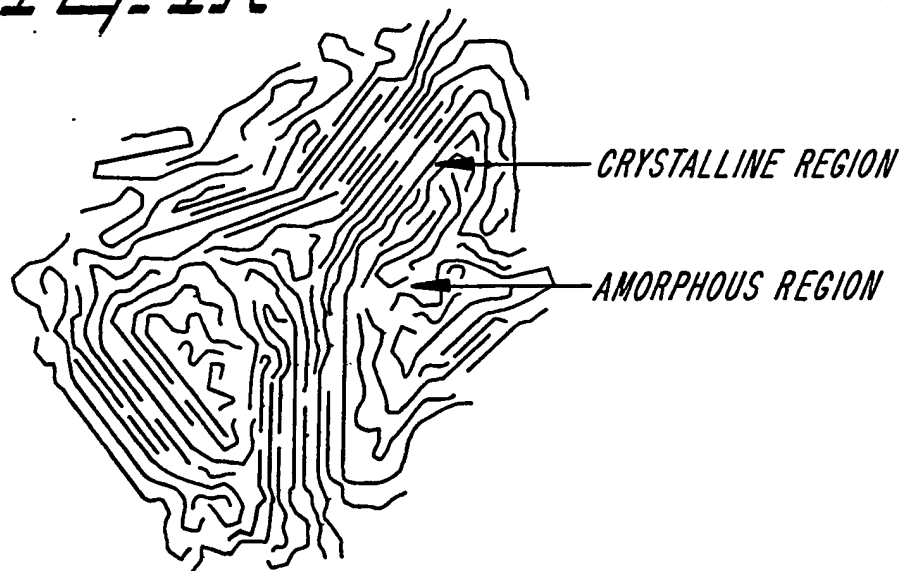
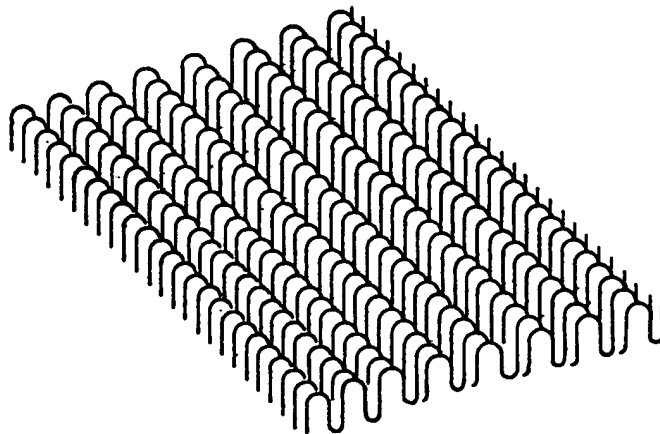
20           23. The drug delivery system according to claim 22 wherein said coating is comprised of agents selected from the group consisting of proteins, surfactants, antibodies and host receptor site specific drugs.

24. A spherical microporous polymeric network containing a pore incorporated agent therein obtained  
25 according to the method of claim 1.

25. The method for preparing a relatively homogeneous essentially spherical microporous polymeric network of interconnecting channels containing a pore incorporated agent therein

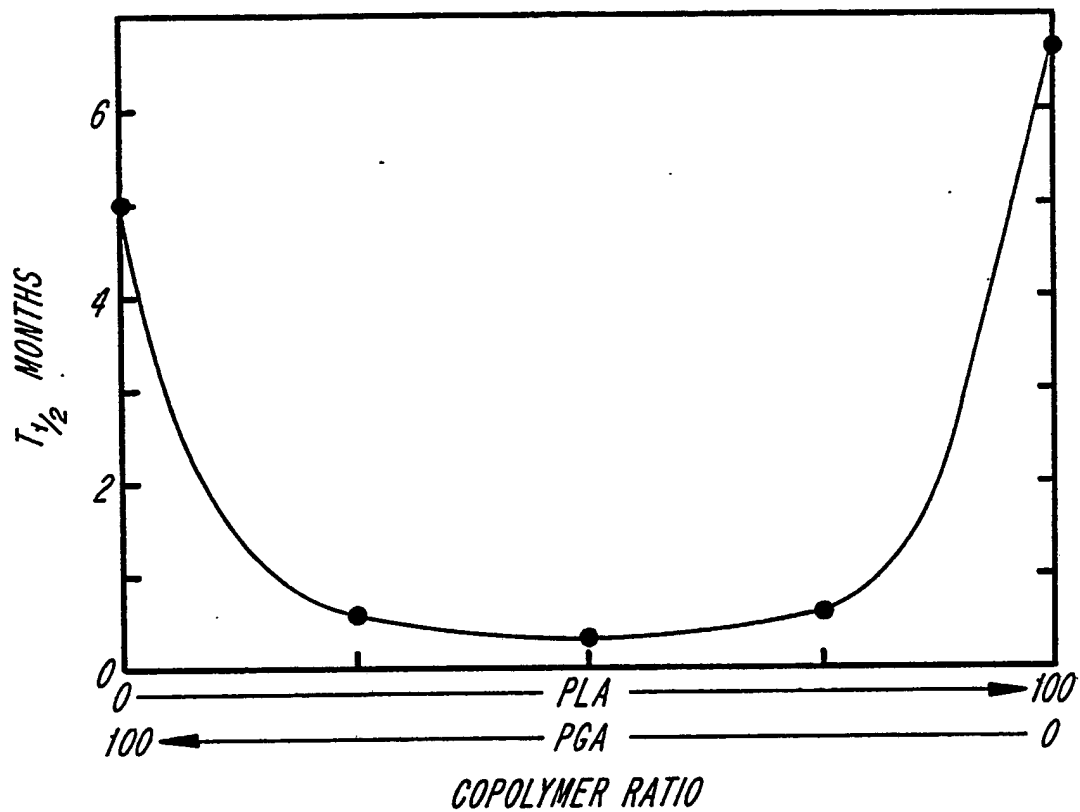


comprising preparing an agent-polymer-solvent dispersed first phase, dispersing said first phase in a continuous solvent second phase to obtain a suspension, removing dispersed first phase solvent from said suspension, and recovering said microporous polymeric network, wherein said removal of solvent from said suspension is by freeze drying of said suspension by a two step freezing procedure to effect separate freezing of first dispersed phase solvent and second continuous phase solvent followed by a two step drying procedure whereby the solvent in both said first and second phases is removed separately allowing recovery of said spherical microporous polymeric network of interconnecting channels.

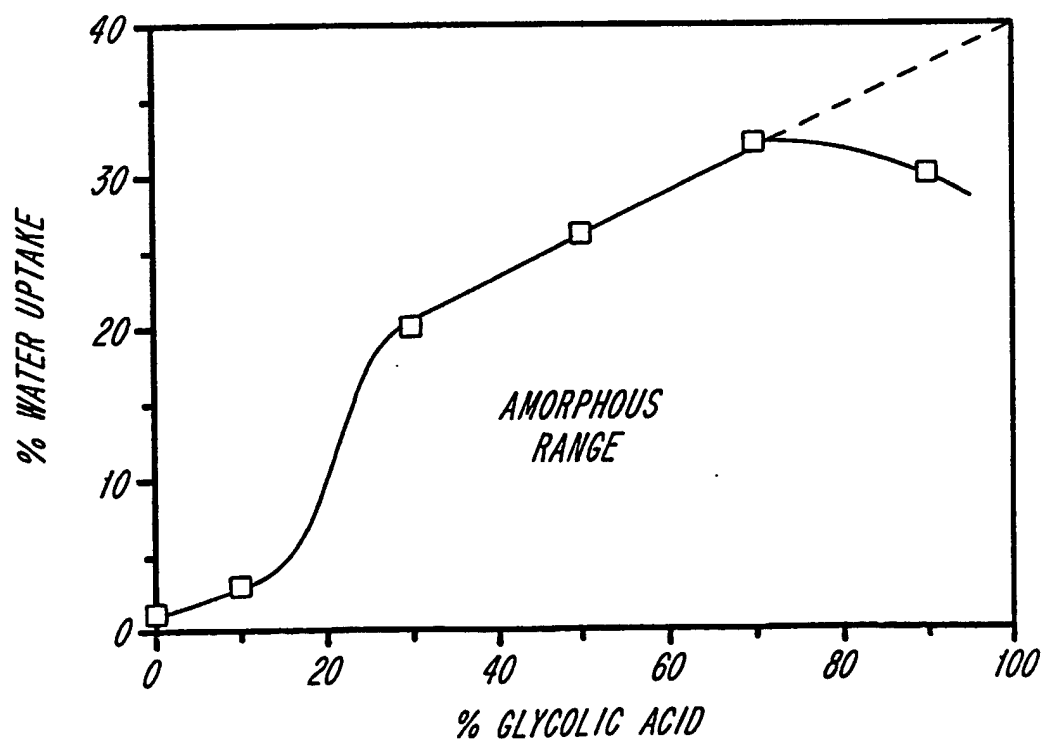
**Fig. 1A****Fig. 1B**

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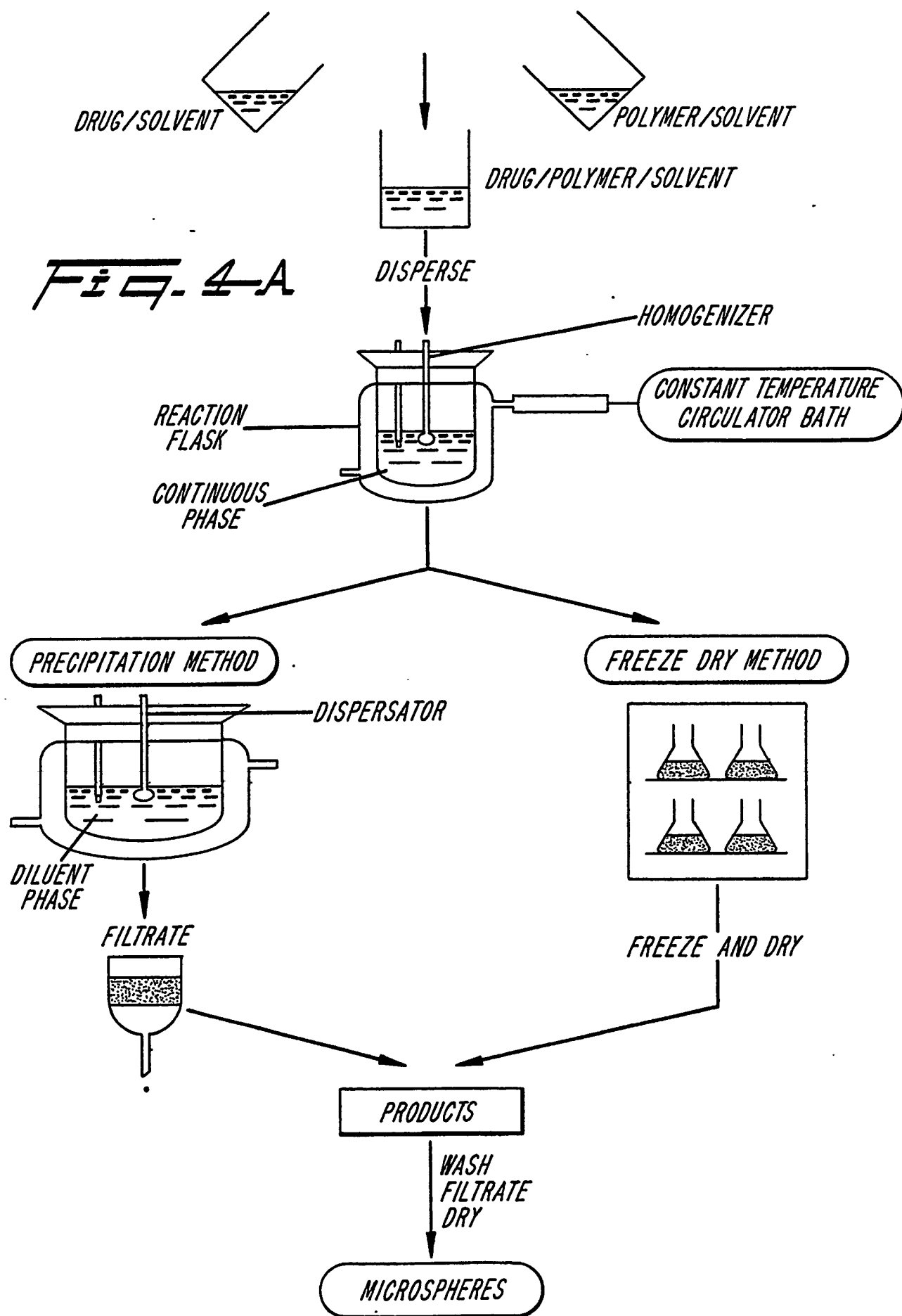
**Fig. 2**



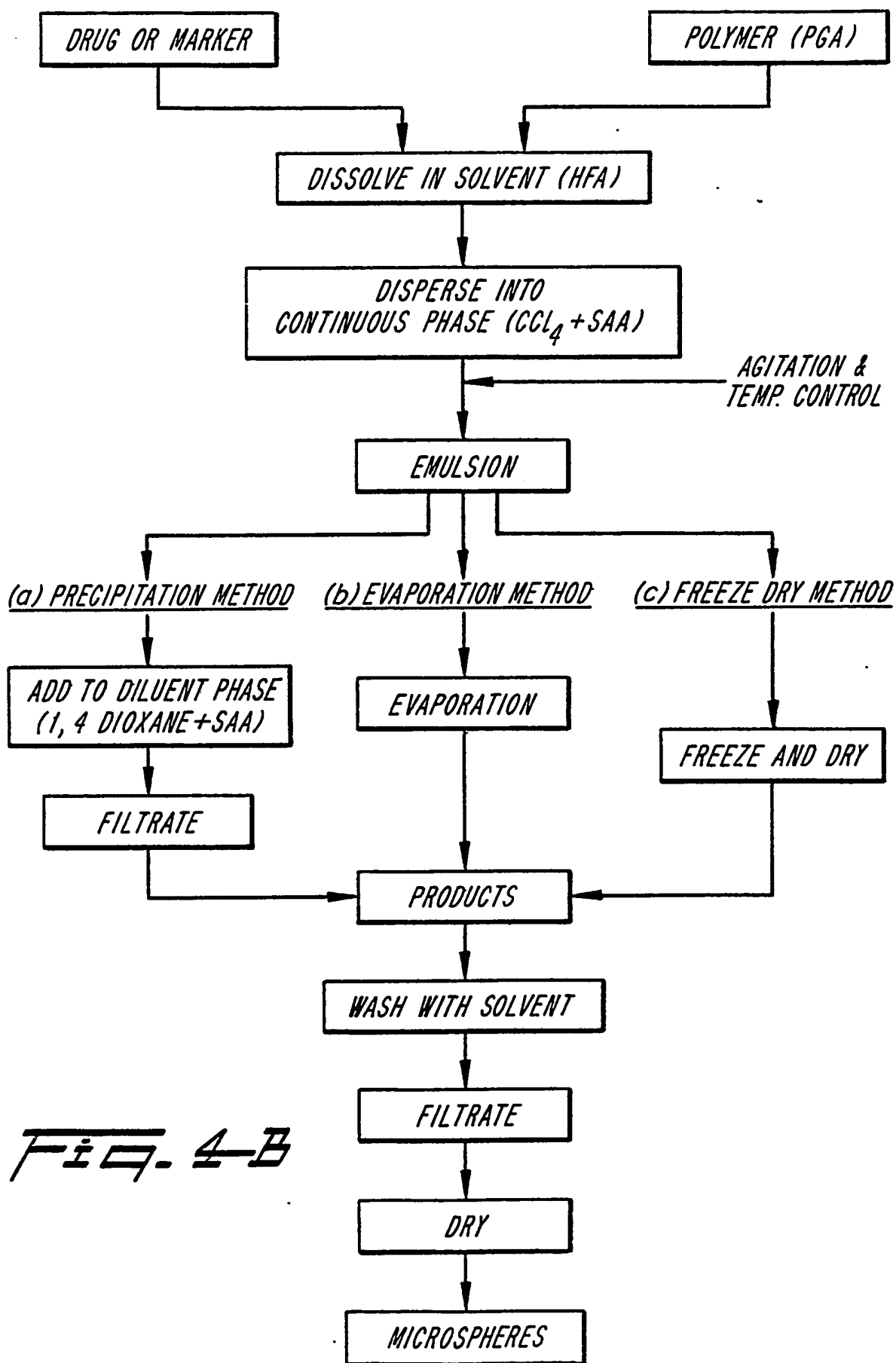
**Fig. 3**

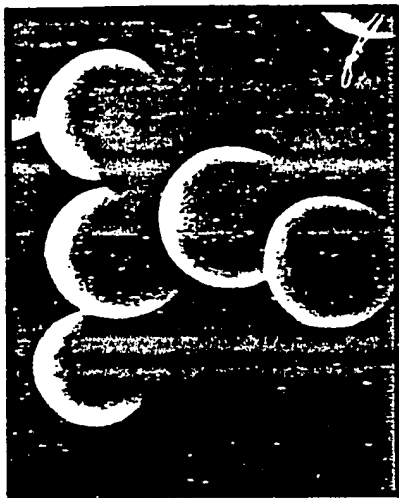


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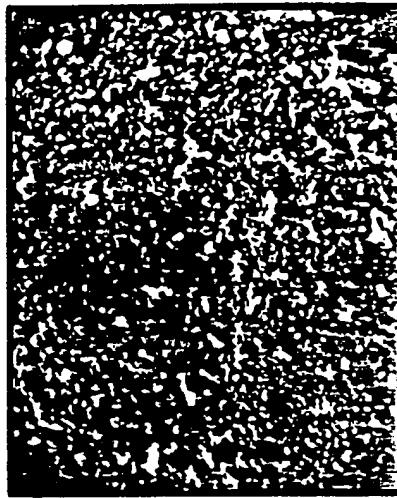


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*Fig. 4-B*



*FIG. 5A*



*FIG. 5B*



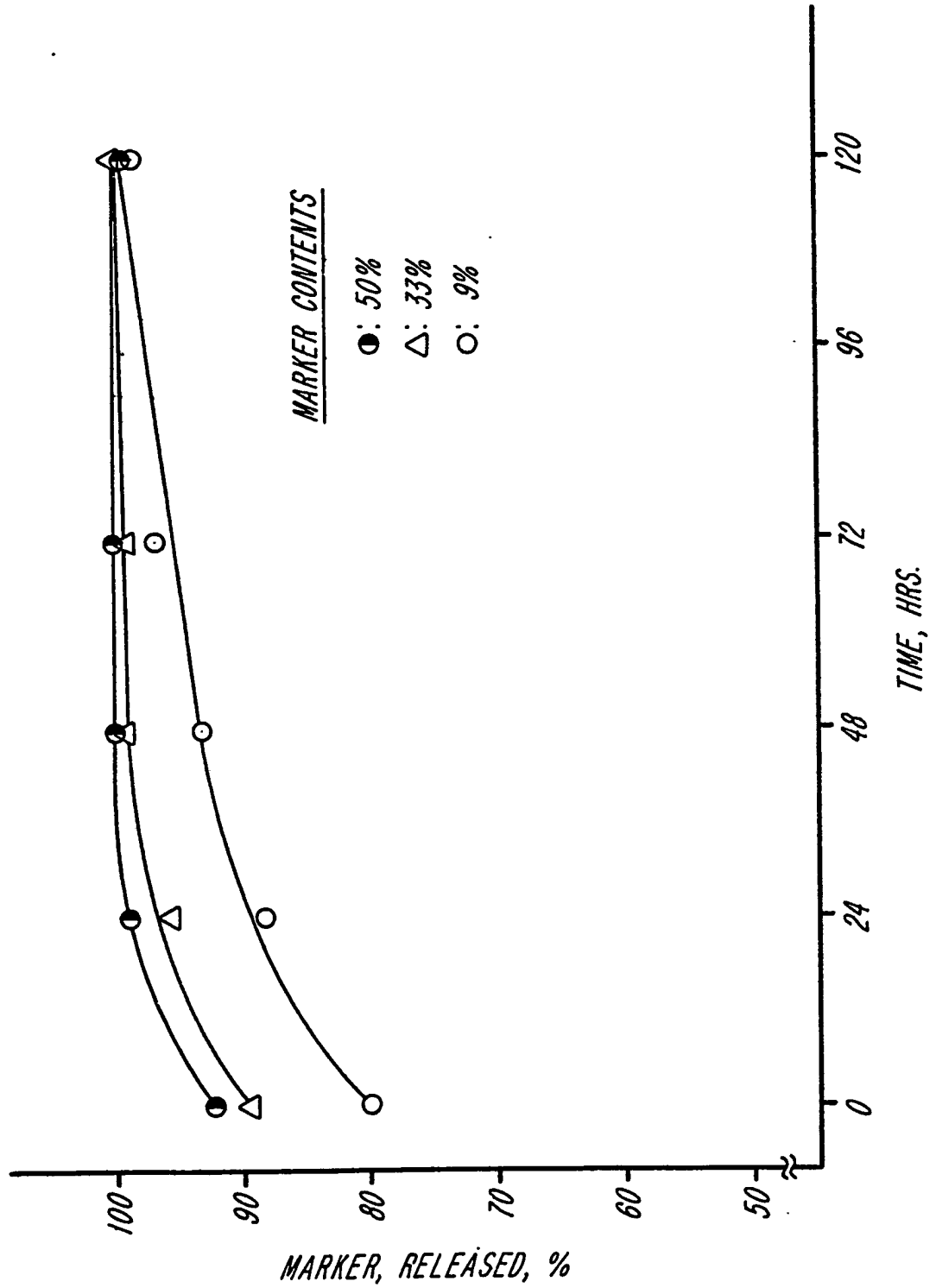
*FIG. 6A*



*FIG. 6B*

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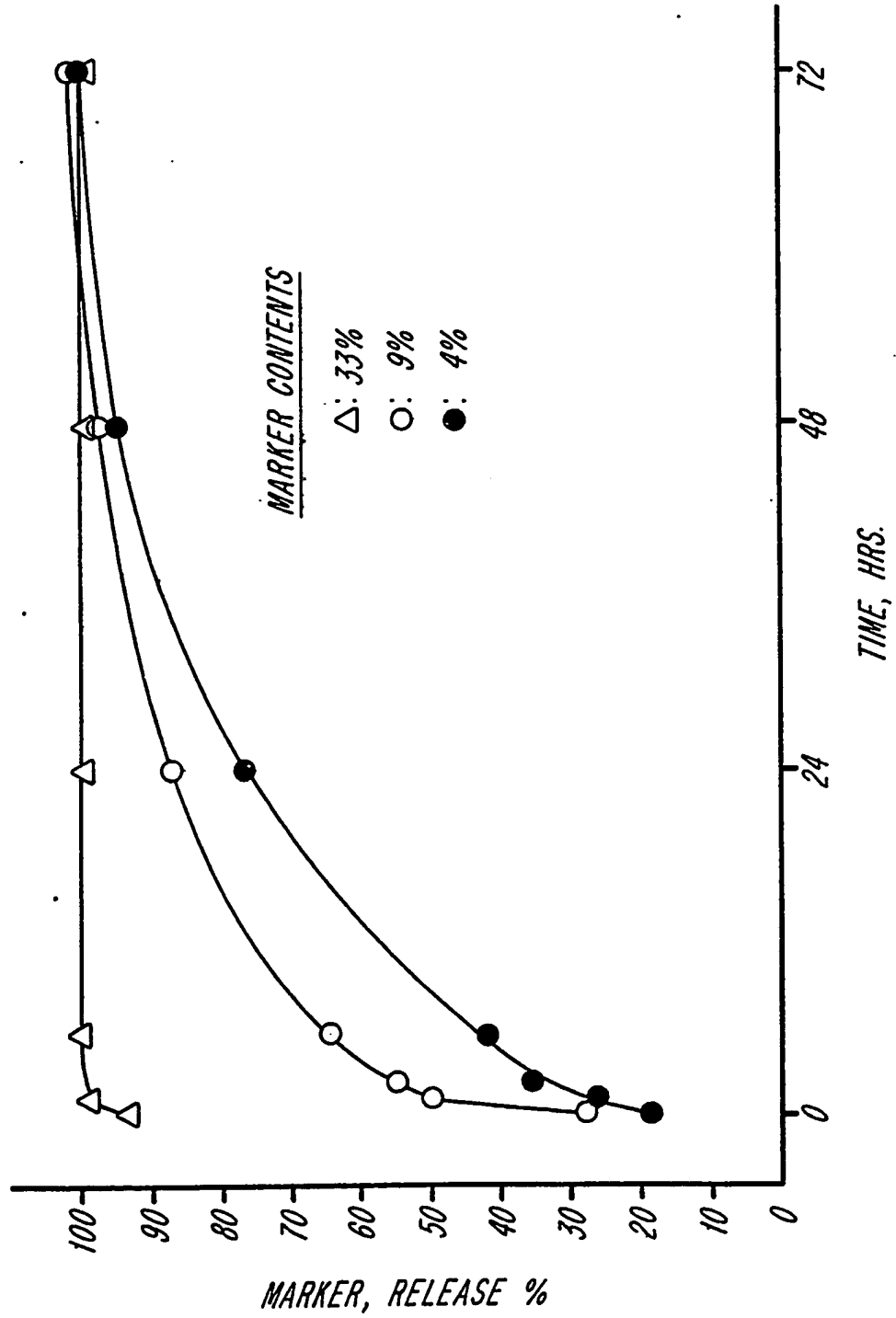
Fig. 7



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Fig. 6

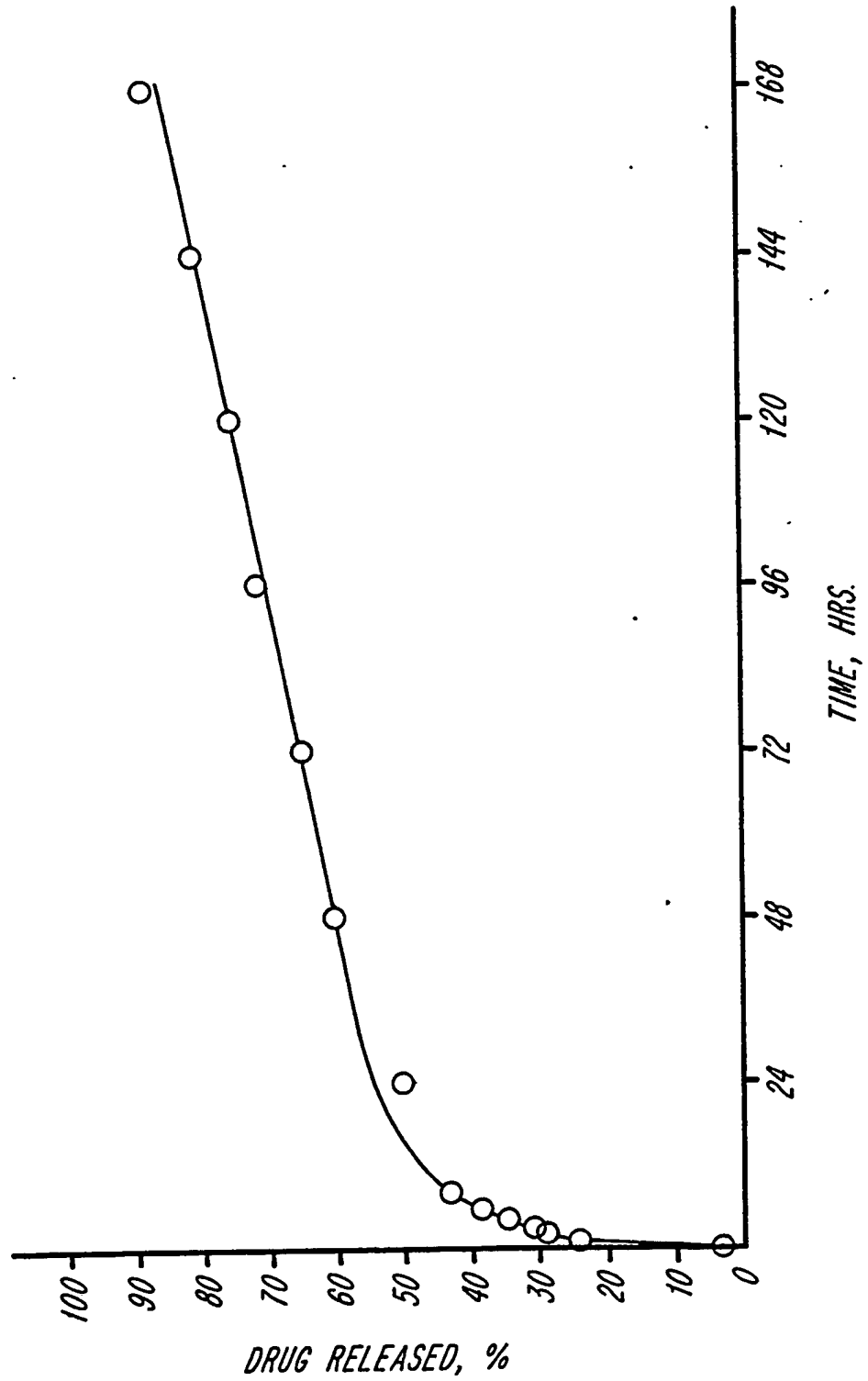


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Fig. 9



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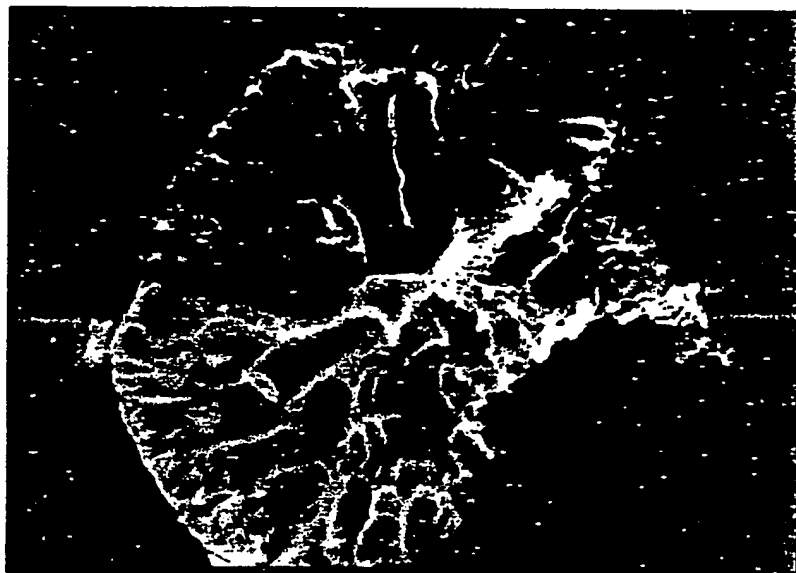
*FIG. 10*



**SUBSTITUTE SHEET**

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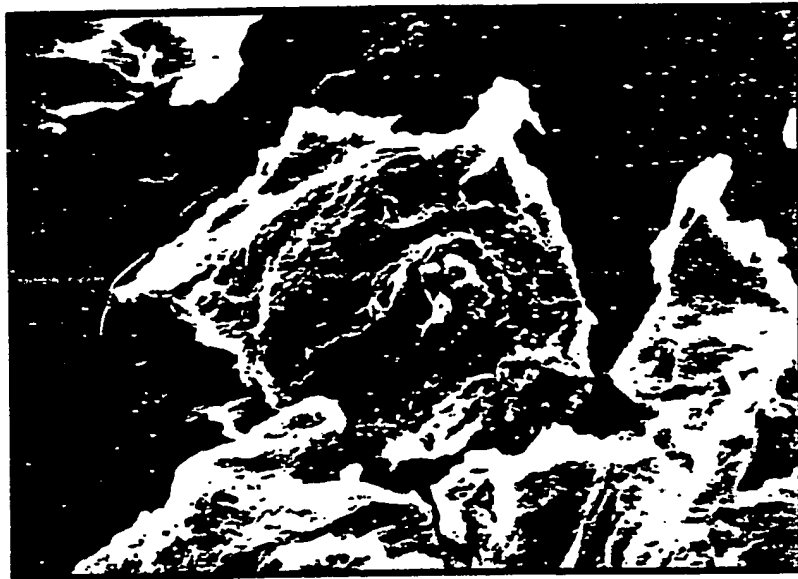
*FIG. 11*



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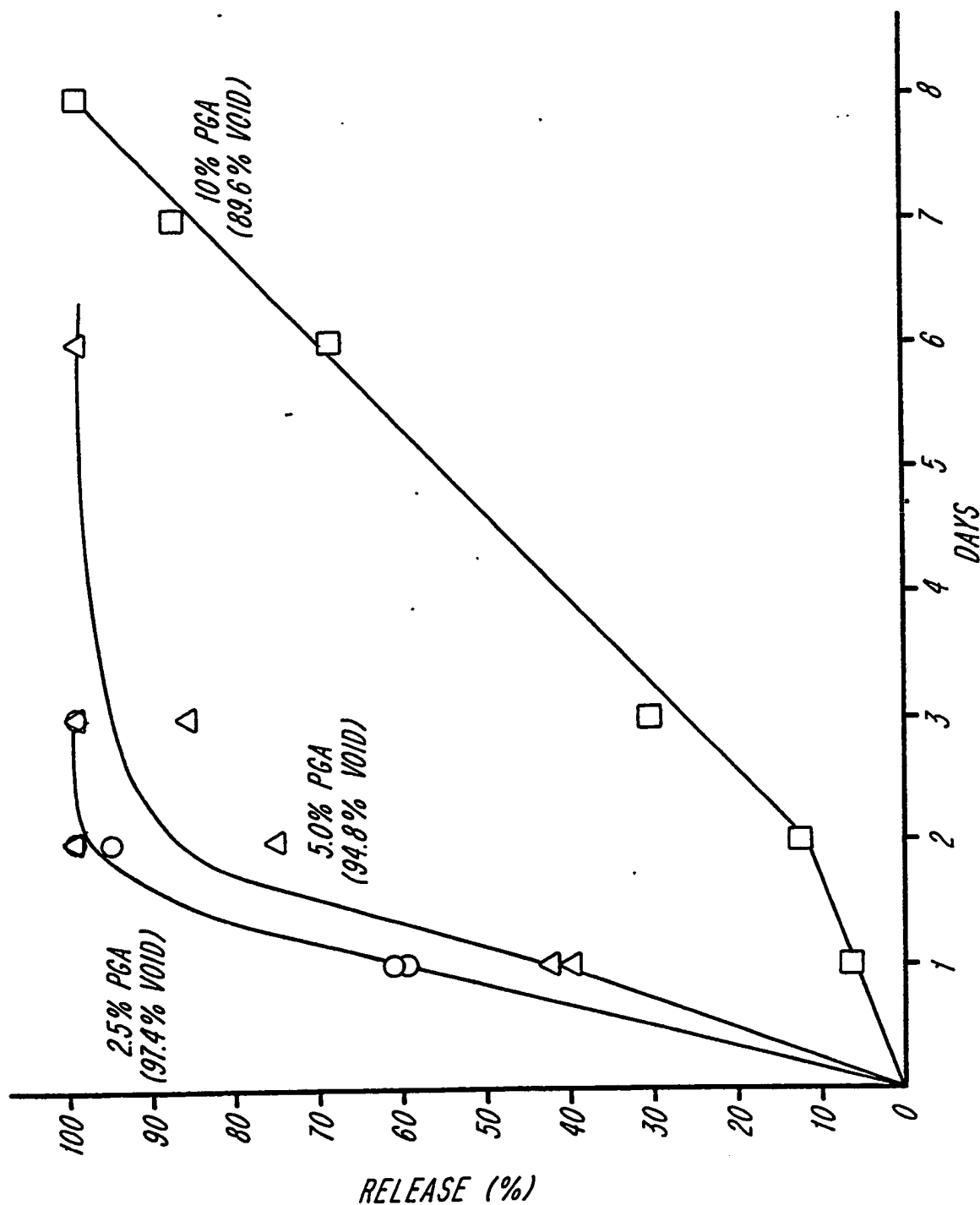
*Fig. 12*



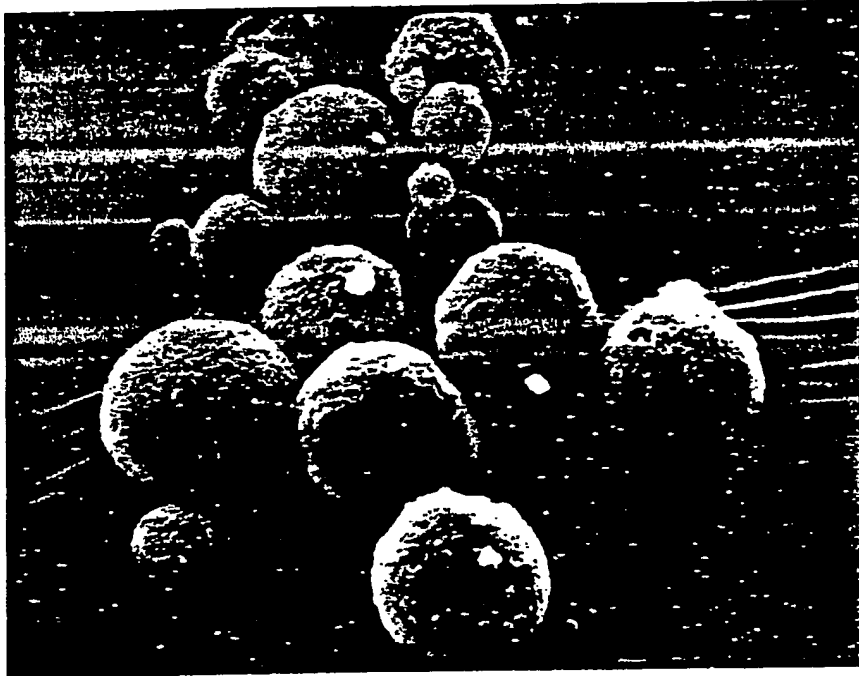
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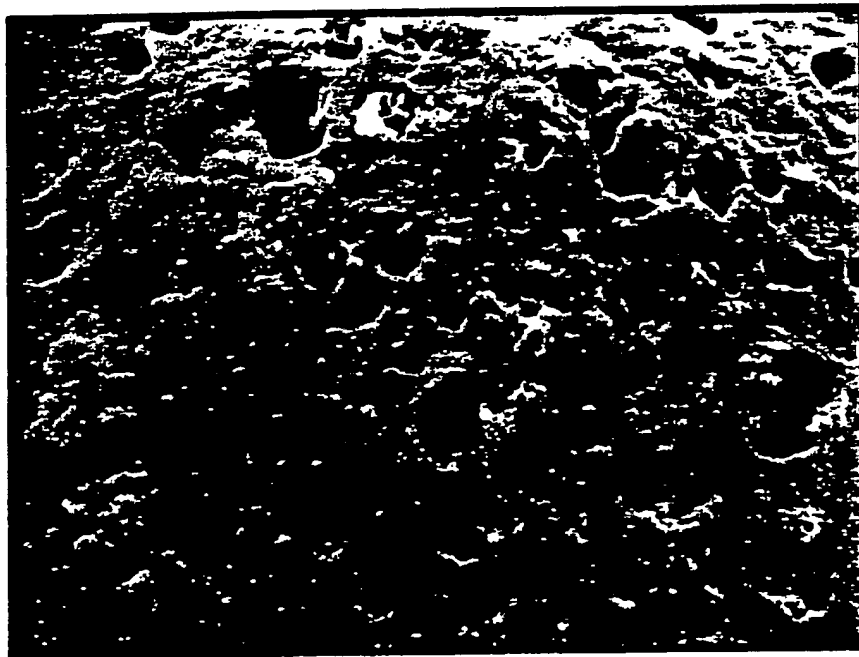
Fig. 1.3



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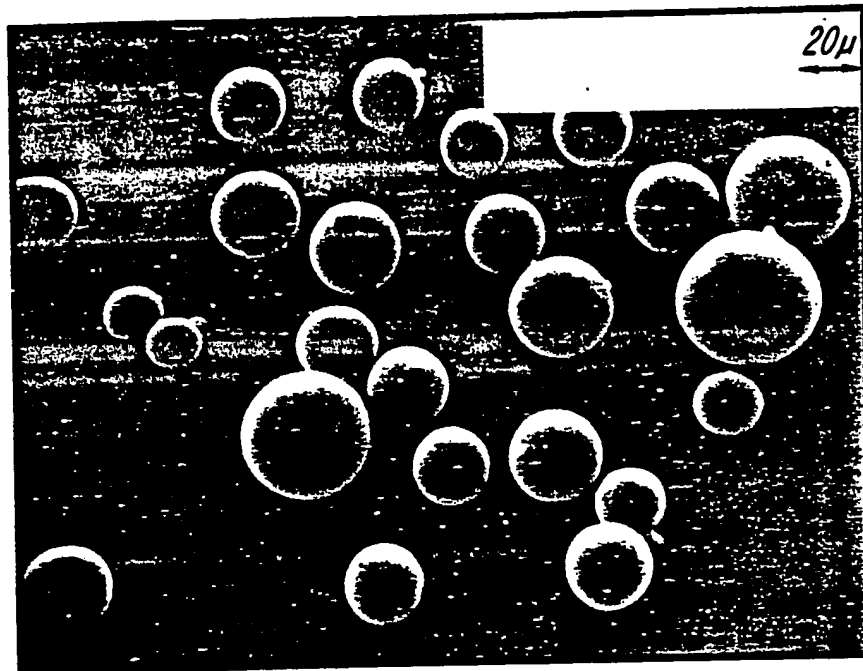
*Fig. 14A*



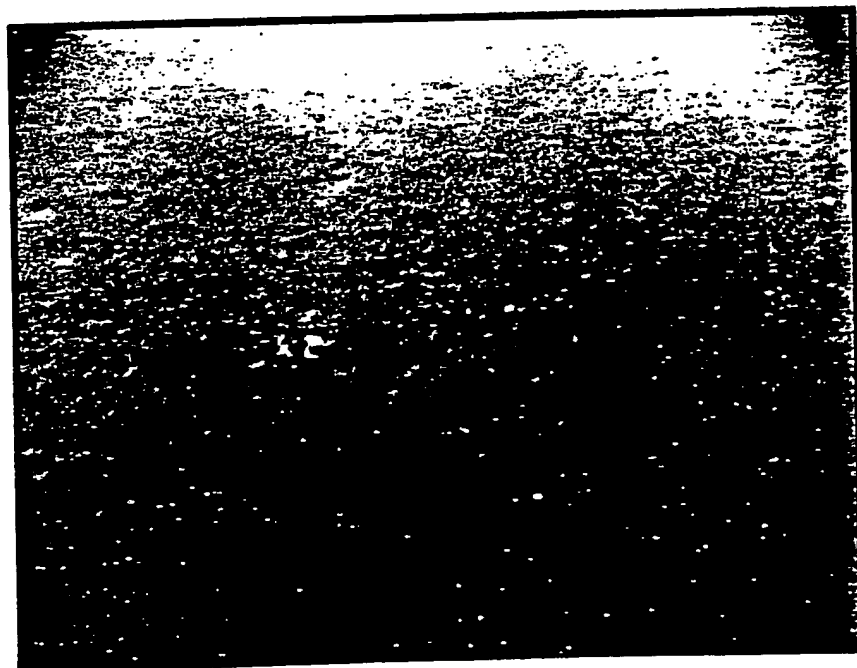
*Fig. 14B*

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*FIG. 15A*



*FIG. 15B*

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 87/03475

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC<sup>4</sup>: A 61 K 9/16; A 61 K 9/50

## II. FIELDS SEARCHED

Minimum Documentation Searched <sup>7</sup>

Classification System

Classification Symbols

IPC<sup>4</sup>

A 61 K; B 01 J 13

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>

## III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup>

Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
T	Chemical Abstracts, volume 108, no. 14, 4 April 1988, (Columbus, Ohio, US), T. Sato et al.: "Porous biodegradable microspheres for controlled drug delivery. I. Assessment of processing conditions and solvent removal techniques", see page 431, abstract 118902x, & Pharm. Res. 1988, 5(1), 21-30	1-25
X	DE, A, 2930248 (BAYER AG) 12 February 1981 see claim; page 2, line 11 - page 9, line 9; page 12, example 7	1,4-6,8-12, 24
Y	--	2,3,13-19
Y	GB, A, 2077693 (SANDOZ) 23 December 1981 see the whole document and in particular page 2, lines 74-77	2,3,13-19
A	--	25
	./.	

\* Special categories of cited documents: <sup>10</sup>

"A" document defining the general state of the art which is not  
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which is cited to establish the publication date of another  
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document is combined with one or more other such docu-  
ments, such combination being obvious to a person skilled  
in the art.

"G" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

29th August 1988

Date of Mailing of this International Search Report

21 SEP 1988

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorizing Officer

P.C.G. VAN DER PUTTEN



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, volume 103, no. 10, 9 September 1985, (Columbus, Ohio, US), P.P. DeLuca et al.: "Preparation of biodegradable microspheres for controlled drug delivery via the parenteral route", see page 321, abstract 76171x, & Expo. - Congr. Int. Technol. Pharm., 3rd 1983, 4, 152-61	
	--	
A	Chemical Abstracts, volume 107, no. 2, 13 July 1987, (Columbus, Ohio, US), see page 67, abstract 8576r, & JP, A, 6245637 (BIOMATERIAL UNIVERSE K.K.) 27 February 1987	25
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X	GB, A, 1198513 (ROUSSEL-UCLAF) 15 July 1970 see the whole document	1-6,8-11, 13,14,16- 19,24
Y		20-23
	--	
Y	Chemical Abstracts, volume 102, no. 24, June 1985, (Columbus, Ohio, US), L. Illum et al.: "Drug targeting using monoclonal antibody-coated nanoparticles", see page 340, abstract 209178h, & Microspheres Drug Ther.: Pharm., Immunol., Med. Aspects, (Pap. Meet.) 1983 (Pub. 1984), 353-63	20-23
	--	
A	EP, A, 0142085 (MOSIER) 22 May 1985 see page 1, line 1 - page 10, end; claims	
	-----	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 8703475  
SA 20477

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 09/09/88  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A- 2930248	12-02-81	None	
GB-A- 2077693	23-12-81	FR-A, B 2484281	18-12-81
		DE-A- 3121983	04-02-82
		JP-A- 57027128	13-02-82
		US-A- 4384975	24-05-83
		CH-B- 648217	15-03-85
GB-A- 1198513	15-07-70	None	
EP-A- 0142085	22-05-85	US-A- 4492720	08-01-85
		JP-A- 60116627	24-06-85
		CA-A- 1220098	07-04-87

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